

**The Relative Contributions of the Premotor and Posterior Parietal Cortices
to Forward Models of Movement**

by

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Abstract

Producing smooth, coordinated movement may seem like a relatively simple process, but it actually requires a complex computational framework in order to reach accurately. It has been hypothesized that the brain predicts the sensory consequences of movement, and indeed, much research has laid down the theoretical framework for this process, however it is unclear how motor planning signals are used to determine the spatial configuration of the limbs. In this dissertation repetitive transcranial magnetic stimulation (rTMS) was applied to candidate sites in the fronto-parietal network to observe how this would affect decisions in a temporal order judgment (TOJ) task under stationary and moving conditions while participants were planning to cross their arms. Previous work has shown that under stationary conditions, error rates increase when participants have their arms in a crossed configuration or are simply planning to cross the arms. Under stationary conditions we observed an increase in TOJ error after rTMS was applied to the posterior parietal cortex (PPC), but not when it was applied to the dorsal premotor cortex (dPMC). However under moving conditions, rTMS caused a decreased in error rates when applied to either the dPMC or the PPC. By contrast, rTMS over a control site (area V4) resulted in no change in error rates under either stationary or moving conditions. Together, these 3 experiments suggest that predictions about the spatial consequences of limb movement use planning signals generated in the dPMC while limb spatial position information is generated within the PPC.

Preface

The following experiment was approved by the UBC Clinical Research Ethics Board, and found the research project acceptable on ethical grounds for research involving human subjects and hereby grants approval.

Ethics Project title: Human reaching and grasping behaviour under the disruption of repetitive transcranial magnetic stimulation (rTMS)

UBC CREB number: H12-00492

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List of Abbreviations

ANOVA – Analysis of Variance

BA – Brodmann Area

BOLD – blood oxygen level dependent

CD – corollary discharge

CHD – crossed-hand deficit

CNS – central nervous system

EEG - Electroencephalography

EMG – electromyography

EPSP – excitatory postsynaptic potentials

FDI -first dorsal interosseous

fMRI – functional magnetic resonance imaging

FSPGR – fast spin gradient

ISI – inter-stimulus interval

IPG – inferior parietal gyrus

IPL – inferior parietal lobe

IPS – inferior parietal sulcus

IPSP – inhibitory postsynaptic potentials

JND – just-noticable difference

M1 – primary motor cortex

MEP – motor-evoked potential

MNI – Montreal Neurological Institute – also the name of the neural coordinate system

MT – movement time

MTG – middle temporal gyrus

PA – peak acceleration

PC – parietal cortex

PPC – posterior parietal cortex

PRR – parietal reach region

PSS – point of subjective simultaneity

PV – peak velocity

RM ANOVA – repeated measures analysis of variance

RMP – resting membrane potential

RMT – resting motor threshold

RT – reaction time

rTMS – repetitive transcranial magnetic stimulation

S1 – primary somatosensory cortex

S2 – secondary somatosensory cortex

SD – standard deviation

SE – standard error

SMA – supplementary motor area

SOA – stimulus onset asynchrony

SPC – superior parietal cortex

SS\SP\SK – steady state\spoiled\segmented k-space

STD – somaesthetic temporal discrimination

STG – Superior temporal gyrus

STTF – Space-time tuning function

TMS – transcranial magnet stimulation

TPA – time to peak acceleration

TPV – time to peak velocity

TOJ – temporal order judgment

TPJ – temporal parietal junction

V1 – primary visual cortex

V4 – Visual Area “4”

VTs – vibrotactile stimulation(s)

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Chapter 1 - Introduction

The ability to accurately perceive the temporal sequence of events is vital to generating movement in a coordinated fashion so that one may interact with the world successfully. In addition, the ordering of successive events in time allows us to make inferences about intention and causality. However, coordinating tactile information from multiple reference frames presents a considerable challenge to the human nervous system. The neural circuitry underlying this ability has been the subject of much debate, with evidence often showing common pathways processing space and time (Battelli et al., 2008). However, the complexity underlying this process becomes readily apparent in patients with neurological damage affecting the sensorimotor system. For example, patients with damage to the premotor area suffer from a feeling that their body has disappeared from awareness (asomatognosia) (Arzy 2006) and difficulty learning to make movements in response to visual cues or verbal commands (Purves 2001).

Quick and complex movements require a continual stream of information regarding the interaction and planning with the environment and the position of the body. Historically, it was thought these interactions were mediated via feedback from the relevant sensory systems providing the central nervous system with updated information concerning the state of the body in space. However, there are a number of problems with exclusively using feedback from the sensory systems to achieve the relatively smooth movements that we observe in humans. One such problem is the large increase in noise from sensory receptors due to self-generated movements. Paradoxically, sensory feedback must be used in order to optimize accuracy during movement, but the introduction of noise creates a large potential for error in both sensory detection and movement accuracy. Secondly, sensory feedback is too slow to account for the

rapidity of observed online corrections. Thirdly, observation of patients with movement disorders indicates that some aspect of movement planning or implementation is disrupted, even if sensory feedback is intact. Lastly, movement is computationally demanding; in an extremely simplified model of the upper limb, in order to achieve a desired postural configuration, there are 2^n degrees of freedom for each muscle (assuming the muscle can be in either a fully-contracted or fully-relaxed state) assuming only 1 muscle per joint. For movements that require considerable adjustment to the base of support due to the redistribution of the center of mass from a moving limb, there are far too many degrees of freedom necessary for the CNS to compute. The solution to these obstacles to coordinated movement has been the proposal that the nervous system makes use of internal models to simplify actions to predict the sensory consequences of movement. A series of novel experiments were performed that demonstrate internal models exist in the brain, and furthermore, that it is possible to disrupt internal models used for self-monitoring without appreciably altering movement kinematics. This thesis provides evidence that the premotor cortex generates planning signals, discusses theories for how the multiple representations in the parietal cortex could be used to reconcile the timing of sensory signals and lastly, demonstrates that specific components of the internal modeling process can be temporarily disrupted.

1.1 Internal Models in the Human Brain

The concept of internal models was developed to simply explain observations of natural human movement in addition to solving the problem of neural computation. Internal models for movement have also been implicated in other contexts, such as eye movements (Colby and Duhamel 1996) and even in pathologies such as schizophrenia (Fournier et al. 2002), suggesting that impairment in internal monitoring of movements results in the perception of externally-

influenced causality. In general, we can classify internal models into two categories: the inverse model and forward model (see Figure 1.1). The forward model will be the focus of this dissertation with a brief description of inverse model because it is a functionally necessary transformation for movement execution and fundamentally-related to movement prediction.

Once the intention to make a movement is generated, the inverse model transforms the kinematics of the desired movement into the kinetic signals required to achieve the desired muscle activation patterns (Shibuya et al. 2007; Wolpert and Ghahramani 2000). This transformation must occur for any voluntary sensorimotor action. However, this mechanism for converting plans to action is too simplified to account for observed behavior. In addition, there must be a signal generated which compensates for movement errors. Interestingly, it has been hypothesized that there are two sources of such signals: one that can be used rapidly and is derived from initial reach plans to make online corrections, and one that is slower and relies on actual sensory feedback.

The discrepancy between the *expected* sensory state that results from the motor command and the *current* sensory state is achieved through the creation of a simultaneous duplicate motor command, termed the efference copy, which is devoted to the prediction of the future state of the limb (Wolpert et al. 2001; Wolpert and Ghahramani 2000). Originally investigated in the context of eye movements, the translation of an efference copy through the forward model results in a signal that predicts the sensory consequences of the movement kinematics associated with the command that was sent to the muscles (see Figure 1.1). This “expected kinematics” signal is compared to the actual sensory signals associated with the movement. By this means, the forward model overcomes the time delays associated with pure feedback control (Mulliken et al. 2008, Shadmehr and Krakauer 2008). In addition, a state estimate can be computed from current

sensory input. Because the exact state of the system is unknown due to the aforementioned feedback and processing delays, the current position of the effector is only estimated (Figure 1.1) (Miall 2007). A state estimate differs from an internal model because it only contains the current conditions of incoming sensations whereas an internal model has established system dynamics that can be used for a given movement. While the models describe observed behavior, there must be a neuroanatomical structure or network that performs a calculation at each stage within the model. It is not currently known exactly which areas would process the expected kinematics calculation, nor is it known the extent to which the potential candidate areas anticipate sensory input.

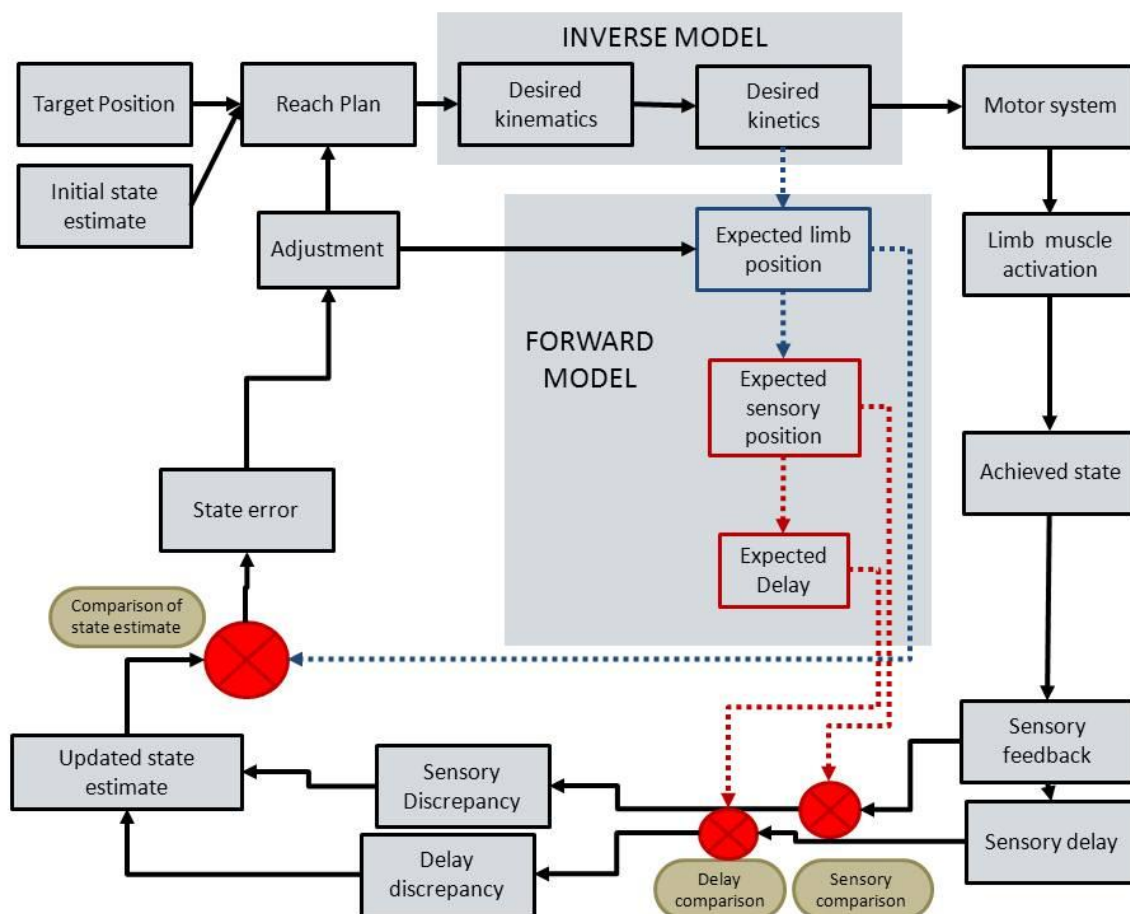


Figure 1.1 - Current architectural theory of forward and inverse models. Adapted from Miall and Wolpert (2008), Sommer and Wurtz (1996), and Desmurget and Grafton (2001). Red circles denote summing

junctions comparisons to compute error. Initial reach plans are generated from a state estimation of the limb and the target position. This information is computed recursively starting with the final position, to generate desired kinematics and eventually desired kinetics suitable for reaching. Efference copy signals are used to compute impending limb position and expected sensory consequences of the movement. To detect any differences between self-generated and externally-imposed stimuli, both the sensory delays and afferent signals are directly compared. The state estimate can then be updated and changes to motor programming can be implemented. The dashed lines indicated processes that are potentially disrupted during experiment (blue processes are potentially disrupted during moving conditions and red processes during stationary conditions).

1.2 Mapping Modeling Functions Based on Neuroanatomy.

There are a number of possible candidate areas (Zilles et al. 2003) which likely contribute to the internal modelling process, with the fronto-parietal network being of particular interest. We might expect that the encoding of a reach plan and the inverse coordinate transformation (Figure 1.1) into useful muscle commands are achieved by the premotor cortex (PMC). Current theories even suggest that the PMC is involved with the generation of the volition to move (Fried et al. 2011). It should be noted that the dorsal portions of premotor cortex and the ventral portions of the PMC can be activated differentially by different tasks. The more dorsal areas of the PMC have been shown to participate in response selection to auditory (Mochizuki 2005) and visual cues (O'Shea et al. 2007), visually guided reaching, as well as spatial updating (Lee and van Donkelaar 2006, van Donkelaar et al. 2002), whereas ventral premotor areas encode bodily postures (Candidi et al. 2008, Urgesi et al. 2007), and grasping movements (Tunik 2008, Davare 2009, 2010). Exactly how the dorsal and ventral sections of the premotor cortex correspond with particular functions of the internal model remains unclear.

A complete movement model of the motor system also requires a cortical area that computes system dynamics with respect to a particular reference frame. Even though the planning components of the PMC have been thoroughly investigated, many of these studies have

examined its connections with the primary motor cortex or its corticospinal projections rather than premotor-parietal connections (Buch et al. 2010). Unlike the PMC, the posterior parietal cortex (PPC) is a reasonable candidate site for processing expectation of the sensory consequences of movement from within the forward model (Figure 1.1). The PPC plays a vital role in the well-documented dorsal visual stream relaying information related to spatial processing in navigation, imagery, and perception (Mast and Jänke 2007). The multifaceted contribution of the PPC to both afferent and efferent mechanisms intuitively suggest that it is necessary for state estimation, however, it is unclear exactly how neurons located in the PPC process information under multiple contexts. Recurrent fronto-parietal connections, many of which project to neurons that descend down the corticospinal tract, provide strong evidence for PPC involvement with the sensory-motor transformations requisite for motor planning (Zilles et al. 2003). These reciprocal connections consequently provide some room for debate as to the exact role of the PPC in planning and execution versus only providing a mechanism from which plans can be made (Anderson 1997).

Although there has not been a consensus on clear demarcations, anatomically, the PPC is comprised of the superior parietal lobule (Brodmann areas 5 and 7) and parts of the inferior parietal lobule (Brodmann areas 39 and 40), (see Vesia and Crawford 2012 for review). Generally, the anterior portion of the parietal lobe (S1) is thought to retain functions primarily pertaining to somatosensory sensation and perception, whereas the PPC is a multimodal integration center associated with using this information along with visual and other relevant sensory signals during motor control. Thus, the PPC is an ideal candidate site where spatial and temporal processing becomes of vital importance, especially as they relate to movement planning.

As a crucial player in the dorsal stream, the PPC receives a generous amount of information related to stimuli present in the visual array. However, visuospatial information about the location of an object with respect to the body is still needed to direct action toward the object. In addition, this visual information must be integrated with other sensory signals associated with the position and movement of the body in space. Raw visuospatial information is then relayed to the parietal lobe to construct both self and environmental representations (Colby and Duhamel 1996). While there exists scores of behavioral and clinical studies to support this theory for the unification of spatial perception, very little has surfaced in support of this idea on a systems or neural network level, suggesting the existence of no singular unified representation but a series of representations of space (Colby and Duhamel 1996; Jäncke 2007). This concept may remain difficult to prove for some time due to the complexity of processing associated with different reference frames. However, because these representations are connected, differentiation between what is a solitary representation and what is a component of a unified representation needs to be investigated further and is beyond the scope of the present experiment. Because movements can be made within the context of a reference frame (e.g. with respect to the whole body, individual body segments, eye position, the environment, and up-coming movements), there must be, necessarily, a place in the brain that computes motor plans for the effectors in an effector-specific manner.

Graziano and colleagues have shown that the ventral premotor cortex retains a representation of arm-, head-, and eye- centered spatial coordinates (1997). Evidence from neural recordings in the dorsal premotor area indicates that the transformations necessary for movement are spatially- and temporally-defined with respect to these modalities (Pesaran, 2006). Takahashi and colleagues (2010) have also shown that the premotor cortex and parietal cortices

participate in processing changes associated with spatial representations, in particular changes to the relative location of the limbs. The multiple reference frames for efferent motor planning signals arising in the premotor cortex and multiple reference frames for afferent sensory signals within the parietal cortex suggest an intimate functional interconnectivity, which is congruent with previous findings indicating that movement planning can bias spatiotemporal judgments (Hermosillo 2011; Ritterband-Rosenbaum et al. 2014).

1.3 Temporal Order Judgment

Determining the timing of sensory signals implies the performance of chronometrics by some cortical structure or structures, but despite the clear need for temporal discrimination, the neural mechanisms underlying timing or time processing are poorly understood. In laboratory settings, temporal processing and the related prediction of cutaneous stimuli during movement can be probed using temporal order judgment (TOJ) tasks. In such tasks, two stimuli are presented in succession and the participant is asked to make a decision as to which appeared first. TOJ tasks often make use of visual (Bachmann et al., 2004; Rutschmann, 1966, Woo 2009), auditory (Hirsch & Sherrick, 1961), or combined audiovisual (Spence et al., 2001; Zampini et al., 2003) modalities and the neural mechanisms underlying TOJ decisions in these modalities are starting to be investigated (Davis et al., 2009). Yamamoto and Kitazawa (2001a,b) have shown that in a cutaneous TOJ task, when the hands are uncrossed the accuracy of these decisions approach 50% chance only at very short (<70ms) stimulus onset asynchronies (SOA). However, when the hands are in a crossed configuration, much longer SOAs (as long as 600ms) are required to achieve accurate judgments (see also Shore et al. 2002, Craig and Belser 2006; Schicke and Roder 2006; Petersen et al. 2003; Oliveri et al. 1999; Azañón and Soto-Faraco 2007; Shibuya 2007). It has been suggested that this “crossed-hand deficit” reflects the

systematic influence of a hand-centric or body-centric reference frame on attempts to construct an accurate somatotopic representation to localize the stimuli by the brain (Craig & Belser 2006; Azañón & Soto-Faraco 2007). Taken together, these studies have demonstrated that an interaction exists between the perceptual decisions regarding the timing of cutaneous stimulation delivered to the hands and the position of the hands with respect to each other.

Because the timing of stimuli can be influenced by the relative position of the hands, it is possible that processing in the sensorimotor control regions of the cerebral cortex influences the temporal perception of impending sensory stimuli during movement planning. A TOJ task can act as a probe of this mechanism as it has previously been shown to be influenced by the relative position of the limbs (Yamamoto and Kitazawa 2001, Shore and Spence 2001) and even the impending final position of the limbs during movement planning (Hermosillo et al. 2011).

Findings from this experiment could help explain the cortical mechanisms for the behavioral phenomenon of haptic mislocalization, a phenomenon where subjects misreport cutaneous stimuli during movement further along the trajectory of movement. (Dassonville 1995), and suggest that the act of planning a movement can be systematically influenced by the spatial localization of the limbs.

Because vibrotactile TOJ tasks are so markedly affected by the relative position of the hands, the premotor cortex (PMC), well-known to be essential in sensory-guided movements, most likely plays a major role in the underlying signal processing in this modality as well (Walsh 2003). Even though the PMC has been shown to be activated during the planning stages of movement, it is not known whether the activation corresponds with the planning associated with sensory prediction. Because the PPC is hypothesized to play both a crucial role in constructing

spatial representations based on somatosensory sensations under stationary conditions, it is expected to be functionally necessary for sensory prediction during movement.

The ability to predict the sensory consequences of movement must involve at least two elements: first, a copy of the motor command must be sent to a cortical area that does not directly activate the effector; and second, the efference copy would have to be used within the existing representation of the effector to calculate expected feedback within the current understanding of system dynamics. Any correction to the movement would require an additional element where actual and expected feedback is compared. We can consider this in terms of the computational model of motor control. In Figure 1.1, the inverse model generates motor planning signals within premotor cortex which subsequently relays expected kinematics to the forward dynamic model, and in conjunction with the sensory state of the arm, the parietal cortex can estimate expected sensory feedback. It should also be noted that even though the parietal cortex may contain a representation of motor system dynamics, if a discrepancy arises from expected feedback and actual feedback, this comparison is likely detected by cerebellum (Miall et al. 2007).

To test whether the PMC and PPC contribute to sensory prediction during movement planning, we temporarily disrupted the normal firing pattern of a targeted population of neurons by applying a strong local magnetic field. We used repetitive transcranial magnetic stimulation (rTMS) to temporarily disrupt neural processing in either the right PMC or the right PPC while participants performed a vibrotactile TOJ task. TMS produces a brief magnetic pulse that can affect neural tissue near the gray–white junction (Epstein et al. 1990) at an estimated penetration depth of roughly 2–3 cm (Rudiak and Marg 1994) and a spatial resolution of approximately 0.5 to 1 cm (Brasil-Neto et al. 1992). When delivered at the appropriate location, it can disrupt task

performance in a systematic manner. By targeting multiple cortical regions we can determine how each contributes to the neurophysiology of forward modeling and sensory prediction associated with movement.

1.4 Hypothesis and Predicted Results

We propose to resolve specific components of sensory state estimation during the planning and execution of movement and to determine how these components are implemented in the PMC and PPC. Based on the available evidence, we assume that the PPC receives incoming information regarding expected kinematics from the PMC and that both are involved in the construction of the forward model(see Figure 1.1, yellow box). We also assume that the PPC, but not the PMC, is involved in state estimation. Finally, we assume that our control site (V4) will not be involved in either of these processes. Given these assumptions, the following hypotheses can be put forward:

Hypothesis 1a: When planning to cross the arms, error rates in the TOJ task following rTMS of the PMC will be decreased.

Hypothesis 1b: When planning to cross the arms, error rates in the TOJ task following rTMS of the PPC will be decreased.

Hypothesis 1c: When planning to cross the arms, error rates in the TOJ task following rTMS of the V4 will be unaffected.

Hypothesis 2a: When not planning to cross the arms, error rates in the TOJ task following rTMS of the PMC will be unaffected.

Hypothesis 2b: When not planning to cross the arms, error rates in the TOJ task following rTMS of the PPC will be increased.

Hypothesis 2c: When not planning to cross the arms, error rates in the TOJ task following rTMS of the PPC will be unaffected.

These hypotheses will be examined by comparing the TOJ error rates prior to vs. after a period of rTMS to each of the targeted sites. They are based on a number of assumptions regarding functional differences between PPC and PMC in the predictive processes underlying movement control. In particular, if the efference copy drives the prediction error rate, the difference from pre to post TMS over the PMC will only be affected under the moving, but not the stationary conditions. We may, however, observe changes to movement parameters after stimulation of the premotor cortex as it has been shown that TMS applied over the premotor cortex can modulate motor output (Koch et al 2006). For the moving conditions, it is unclear how the movement parameters will be affected if at all by PPC disruption, however TOJ error rates should increase under stationary conditions. We do not expect movement parameters to be changed with V4 stimulation.

This project has several innovative aspects that will provide unique insight into the generation of a forward model of movement. First, the methodology allows for the examination of neural processes in a systematic, non-invasive manner. Additionally, the results of this project will fill a knowledge gap related to the neural mechanisms underlying spatial and temporal perception during limb movement. Moreover, using rTMS to disrupt cortical structures thought to contribute to processing sensory input, will provide unprecedented insight into how this process is implemented in the central nervous system. The current study is novel in that it involves a simple behavioral paradigm in such a way that the resulting behavioral performance will allow insight into the specific circuits associated with predicting the spatial configuration of the limb as predicted from the forward dynamic model. Ultimately, the results from this project

have the potential to inform theories about temporal perception as well as efference copy generation.

Chapter 2: Methods

2.1 Participants

Eleven healthy, right-handed participants, [age 28 years \pm 5.16, 5 female], drawn from the University community participated in the experiment. One female participant could not complete the protocol due to scheduling conflicts, and was excluded from analyses. The remaining ten participants that participated had no known neurological or peripheral deficit, were not taking medication that affected vision, cutaneous sensitivity, or manual motor control, did not have a history of epilepsy or other neurological dysfunction, had no non-removable ferrous material in or around the head, nor use of any cardiorespiratory device. All participants reported normal or corrected to normal vision. All experiments were approved by the University of British Columbia Clinical Research Ethics Board prior to participation.

2.2 Experimental Design

Each participant completed 3 sessions during which 1 of 3 cortical sites was targeted with rTMS. Prior to and after the rTMS, participants performed a block of bimanual TOJ task trials. Each of the sessions was completed on different days separated by at least 5 days.

2.3 TOJ task

During each testing session, the participant was seated at a table and asked to make a judgment as accurately as possible about which of two vibrotactile stimuli separated by a 100ms time interval was presented first (see Figure 2.1 A). Stimuli were delivered by a piezoelectric device controlled by three 5V pulses with 2ms interpulse intervals producing a 1mm displacement of a 2mm² contact point. The stimulators were attached with straps to the distal pad of the right or left index finger. In the moving condition, a start tone cued the participant to begin

moving (Figure 2.1 B) and the 1st vibrotactile stimulus was delivered 250ms after the start tone. This delay was chosen because previous work has demonstrated that it causes a maximum increase in TOJ error rates (Hermosillo et al 2011). Upon hearing the tone, participants were instructed to cross his or her arms as quickly as possible from starting targets (1.5cm diameter) positioned 10cm on both sides of the midline to targets in the opposite hemispace (5 cm from the midline) (Figure 2.1 B). Participants started in an uncrossed posture on the outside targets and moved their hands across the midline to the opposite target. By contrast, in the stationary condition, participants were still presented with a GO tone, but kept their hands on the start target throughout the trial. At the end of each trial, participants verbally indicated (“right” or “left”) which hand was stimulated first. Throughout each trial, hand motion was monitored by an Optotrack Certus system (Northern Digital Inc., Waterloo Ontario) which recorded (500Hz) the position of two infrared-emitting diodes (IREDs) attached to the distal phalanx of each index finger. Within each session, participants performed 4 blocks of trials: 2 blocks (stationary then moving) before rTMS and 2 blocks afterward (identical to pretest).

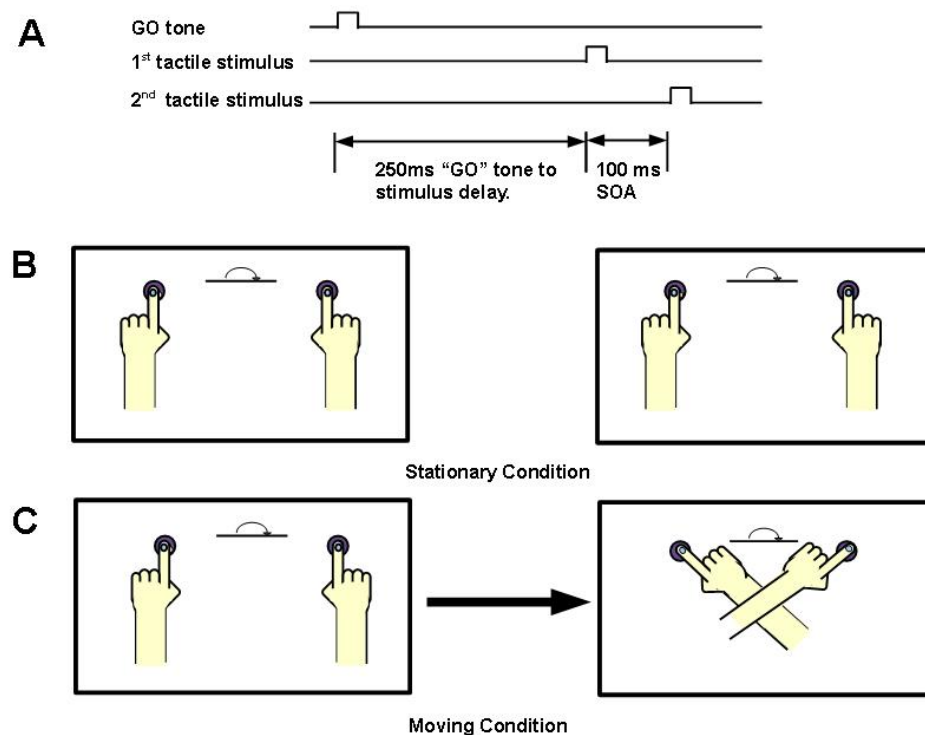


Figure 2.1: Schema of Arm-crossing with Temporal Order Judgment Task. **A:** A tone was presented and the 1st vibrotactile stimulus was delivered 250ms afterward followed 100ms later by the 2nd vibrotactile stimulus. **B:** In the stationary condition, participants kept their arms stationary and reported which stimulus they felt first. **C:** In the moving condition, participants crossed their arms as quickly as possible after they heard the tone. After crossing, they reported which stimulus they felt first.

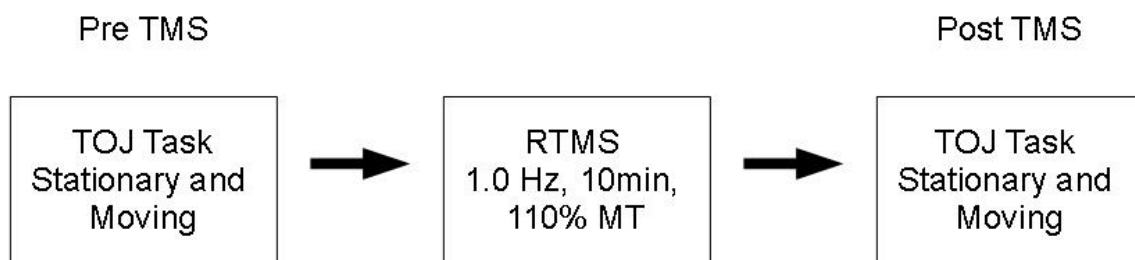


Figure 2.2: Experimental Design: Participants completed the stationary and moving conditions of the TOJ task prior to and after a 10 min period of rTMS delivered at 1.0 Hz over the right PMC, PPC, or V4.

2.4 Transcranial Magnetic Stimulation

In separate sessions, the right PMC, PPC, or V4 was stimulated with 1.0Hz rTMS for 10 minutes through a 70mm figure eight coil (Magstim Super Rapid² (Magstim[®], UK)). This stimulation frequency has been shown to disrupt or inhibit normal neural processing (Boyd and Linsdell 2009; see Fitzgerald 2006 for review), and has been used to decrease proprioceptive acuity when applied over regions of the parietal cortex (Balslev et al. 2004). Stimulation intensity was determined on an individual basis by finding the motor threshold for each participant after localizing the hot point of the hand region in the motor cortex. The motor threshold is defined as the lowest stimulation intensity at which a motor-evoked potential (MEP) of 50 μ V from the first dorsal interosseus (FDI) muscle of the contralateral hand can be reliably evoked (Petersen et al. 2003) in 5 out of 10 trials and is reported as a percentage of stimulator output (2T Magstim Super Rapid²). Monopolar electromyography (EMG) was monitored at 10kHz for this purpose (Rouge Research Inc. Canada), with an inter-electrode distance of about 1 inch, with positive electrode on the muscle belly of the FDI, the negative electrode over the distal head of the right second metacarpal, and the ground at the styloid process of the ulna, with each TMS stimulation recorded with a frameless stereotaxic guidance system (see Section 2.5 below). Peak-to-Peak EMG amplitude was calculated for each MEP, using the absolute value of the difference between the maximum positive elicited voltage followed by the negative volley within a time window of 15-65ms after the TMS pulse.

MRI-guided rTMS was used in this experiment instead of surface anatomy, or stimulation based on the International 10-20 electroencephalography (EEG) system, to add precision and verification (see Section 2.5) to the coil placement. During the experimental

sessions, the stimulator output was set to 110% of the motor threshold and delivered over the targeted site. In all sessions, the coil was held in place at the stimulation site with an armature system and contact ensured by the experimenter. In addition, the head was stabilized with a chin rest. For the PMC, the handle of the stimulating coil was oriented posteriorly at a 45° angle to the midline. For the PPC, the coil handle was oriented toward the external occipital protuberance. For the V4 stimulation, the coil handle was oriented tangential to the surface of the skull, with the coil handle pointing up, parallel with spinal cord and sagittal suture. V4 was selected as a control site because it has been shown to process visual shape and color information (Tanigawa 2010) and, therefore, would be expected to contribute minimally, to predicting sensory consequences of movement.

2.5 TMS Site Verification

High-resolution T1-weighted structural brain images were acquired for each participant in a GE 1.5T HDxT 16 channel MRI scanner. Images were collected with an ultrafast spoiled gradient echo 3D (3D FSPGR), with sequence variants SS\SP\SK, and a slice thickness of either 2mm (4 participants) or 1mm (6 participants). The MRI images were then used to perform a digital 3-dimensional reconstruction of the head and brain using specialized conversion software (Brainsight 2.x software (Rouge Research Inc. Canada)). The reconstruction was verified to follow the contours of the surface of the cerebellar and cerebral cortex, under the dura matter, excluding space occupied by the cerebrospinal fluid. A frameless stereotaxic system (also made by Rouge Research Inc. Canada) was used to co-register anatomical landmarks on the skin with the underlying anatomy so that the location of the TMS site could be identified for each participant in MNI coordinates. For the PMC, the frontal cortex was targeted just anterior to the precentral gyrus and posterior to the arcuate sulcus. The coordinates for PMC stimulation [30,-4, 45]

(Mayka et al. 2006) are in the lateral aspect of Brodmann area 6, while for the PPC we stimulated medial to the intraparietal sulcus, and anterior to the parieto-occipital sulcus [-32, -54, 62; Brodmann area 7]. In either case, if the coordinates were within the cerebrospinal space or the white matter tracts, adjustments were made to ensure targets were within the grey matter region of the cortex. The location of the stimulation site was visualized and maintained throughout the experimental session using the stereotaxic system.

In humans, there is still much debate as to exactly what specific types of visual information area V4 receives, however within BA 19 it appears that there is a consensus that in the cortical region anterior to V3, closer to the lateral occipital gyrus, (generally accepted as V4 or hV4 [“h” for “human”]) information is arranged retinotopically (Hansen et al. 2007). The debate may also arise from the fact that no clear consensus has been provided to define boundaries for area V4 (Hansen et al. 2007; Tanigawa et al. 2010; see Roe et al. 2012 for review).

MNI coordinates are given for the stimulation site on the scalp averaged across participants (see Tables 1 and 2). This form of stereotactic-guided stimulation produces a high level of accuracy with each stimulation site. Variable error (in absolute mm) for each stimulation site was averaged across participants as well as angular error based on an ideal target vector placed tangential to the surface of the cortex.

2.6 Experimental Conditions:

Conditions were run in counterbalanced sessions across participants, one for each of the three stimulation sites (PMC, PPC, and V4). In each condition, the moving and stationary versions of the TOJ task were completed prior to and after a 10 minute period of rTMS at 1.0 Hz at 110% RMT. Each of the 3 sessions lasted approximately 1 hour.

2.7 Data Analysis

For each participant and condition, the main dependent variable of interest was TOJ error rate. In addition, for the moving trials, we determined reaction time (RT), movement time (MT), time to peak velocity (TPV), peak velocity (PV), peak acceleration (PA), time to peak acceleration (TPA), and end point accuracy (Lanshammar 1982). Each of these dependent variables was examined using a 4-way repeated measures analysis of variance (RM-ANOVA) (2 [conditions: stationary vs. moving] x 2 [hand stimulated first: right vs. left] x 3 [stimulation site: PPC vs. PMC vs. V4] x 2 [time: pre-test vs. post-test]). Statistical significance threshold was set at 0.05. Post-hoc t-tests were performed with a Bonferroni correction for multiple comparisons.

Chapter 3 - Results

Note: In the following chapter, figure error bars denote 1 between-subject standard error of mean. In text reference indicate mean \pm 95% confidence interval size.

3.1 TMS site verification and MEPs

The average target error at each site was approximately ± 1.0 mm, demonstrating that within a session (see Table 3.1), target precision was maintained. The discrepancy between the cortical targets and the actual stimulated coordinates arises because the targets were placed on the surface of the reconstructed brain (3-6mm peel depth) whereas the coordinates for the stimulated regions represent the actual location on the scalp directed toward the target (Figure 3.1).

Table 3.1 - Targeted Sites for TMS in MNI coordinates averaged across participants. The coordinates for actual stimulation position on the scalp are shown in MNI coordinates. (Values shown in parentheses are average within-subject S.E.)

Brain region	PMC	PPC	V4
Cortical regions targeted	[30, -4, 45] <i>[Mayka et.al 2006]</i>	[-32, -54, 62] <i>[Takahashi et al. 2010]</i>	[31.5, 84.7, -19.7] <i>[Tanigawa and Hadjikhani 2001].</i>
Average MNI coordinates for TMS coil location	[45.16, 3.29, 84.84] (0.229, 0.313, 0.240)	[43.60, -60.05, 85.92] (0.283, 0.355, 0.401)	[48.43, -103.17, -15.81] (0.531, 0.447, 0.678)
Distance to target (mm)	18.83 (0.219)	21.851 (0.285)	25.16 (0.540)
Target error (mm)	0.9431 (0.244)	0.894 (0.318)	1.238 (0.378)
Angular error (degrees)	3.376 (0.265)	3.199 (0.304)	9.59 (0.972)
EMG peak to Peak (μ V)	82.13 (60.535)	31.400 (6.133)	33.03 (6.825)

The motor threshold for participants was tested independently for each session, and was not statistically different between testing sites. (dPMC vs. PPC: $t(9) = 0.413$, $p=0.689$; PPC vs. V4: $t(9) = 0.574$, $p= 0.579$; dPMC vs. V4: $t(9) = 0.00$, $p = 1.00$; see Table 3.2).

Table 3.2 - TMS and locations (in MNI coordinates) for motor cortex used to establish motor threshold for each session. NOTE: MNI coordinates correspond with the location on the scalp where the TMS was applied, not necessarily the MNI coordinates of the primary motor cortex.

Brain region	M1 (<i>PMC</i>)	M1 (<i>PPC</i>)	M1 (<i>V4</i>)
Average MNI coordinates for TMS coil location	[51.42, -13.587, 84.01] (0.129, 0.129, 0.143)	[51.65, -11.72, 83.55] (0.691, 0.798, 0.586)	[52.85, -8.130, 78.69] (0.216, 0.420, 0.214)
MEP threshold (% Stimulator Output) \pm S.D.	49.2 \pm 3.081	50.1 \pm 2.9366	49.2 \pm 2.624

TMS target stimulation was significantly more variable in sessions in which area V4 was targeted. This is primarily due to two factors: first, orientation of the TMS coil tracker slightly downward while simultaneously maintaining visibility of an upward-facing head tracker proved challenging for the Polaris camera (Rouge Research Inc. Canada); and, second, at this particular stimulation site the induced current would cause direct activation of the underlying occipitalis and splenius capitus muscles, sometimes causing slight elevation of the chin.

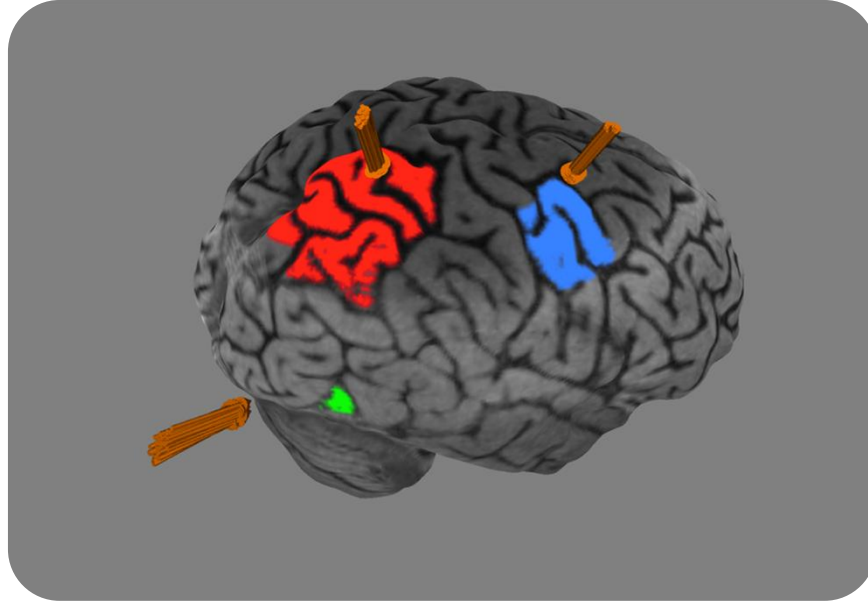


Figure 3.1: Location of TMS pulses applied in real space to brain of an individual participant. The blue region shows the dPMC, the red the PPC, and the green, area V4. The orange arrows show the orientation of the stimulating coil for all 600 pulses within a session overlaid for visual comparison.

3.2 Temporal Order Judgment Error Rates

We observed a main effect of site stimulated, ($F[2,18] = 4.059$, $p = 0.035$, partial $\eta^2 = 0.311$), where PMC stimulation elicited the largest error rate (dPMC: $29.875\% \pm 3.972$ vs. PPC: $19.375\% \pm 3.634$ vs. V4: $19.875\% \pm 3.942$; see Figure 3.2). Post hoc-within-participant contrasts revealed that overall error rates were higher when the dPMC was stimulated compared to V4 ($F[1,9] = 6.023$, $p = 0.036$, partial $\eta^2 = 0.403$, see Figure 3.3). We also observed a significant difference in error rate between stationary and moving conditions ($F[1,9] = 28.099$, $p < 0.001$, partial $\eta^2 = 0.757$), ($12.75\% \pm 3.84$ vs. $33.33\% \pm 3.31$) (Figure 3.3).

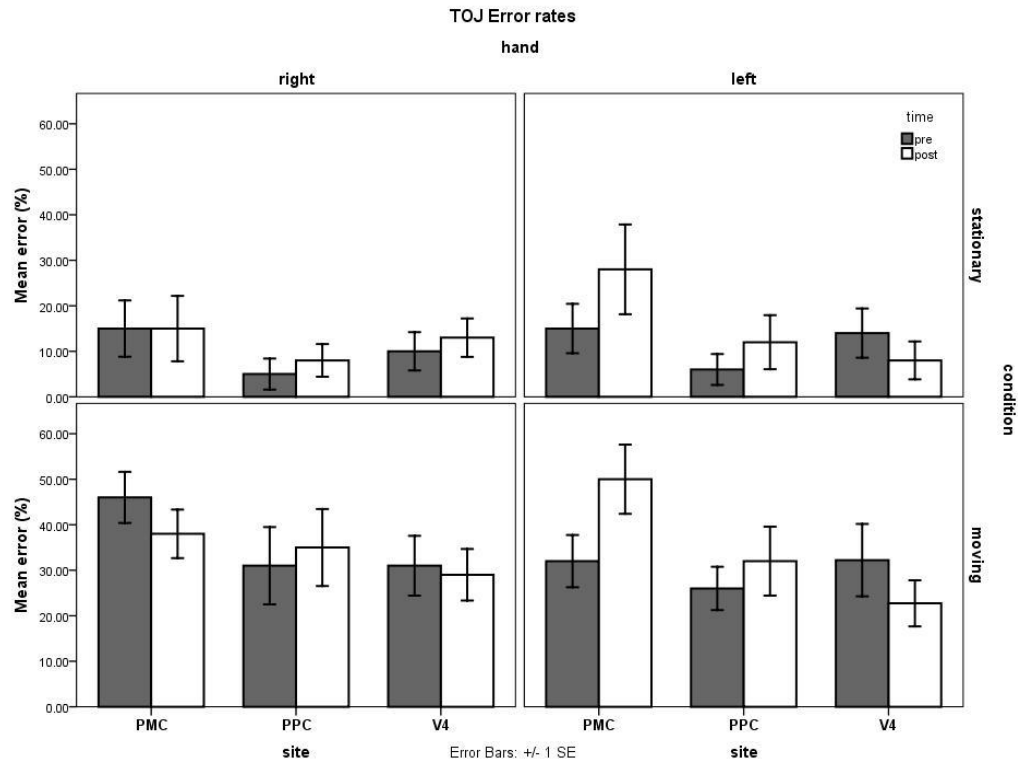


Figure 3.2: TOJ Error rates. Graph depicts mean TOJ error rates for each condition. Pretesting is shown in grey and post testing is shown in white. Error bars represent the between-participant standard error.

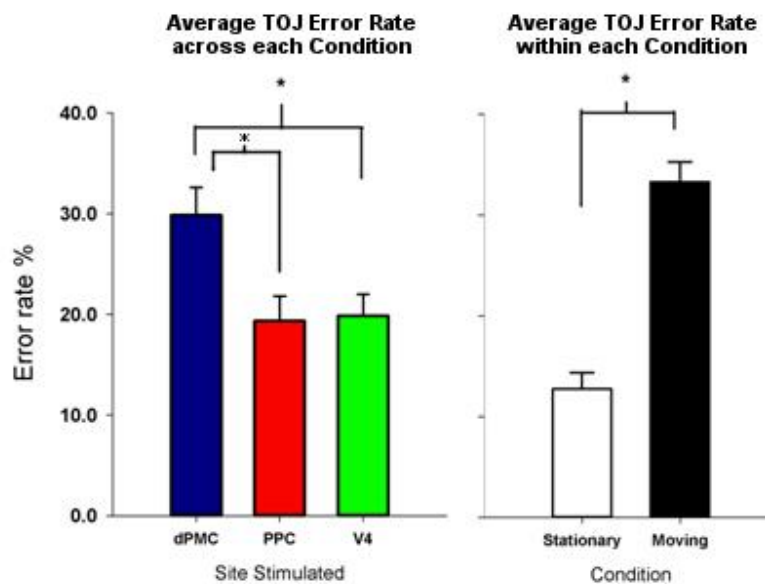


Figure 3.3: TOJ Main Effects: Left: Group means for TOJ error rates at each site stimulated. TOJ errors were averaged across pre- and post- test and moving and stationary conditions. Sessions

in which the dPMC were stimulated are shown in blue; sessions in which the PPC was stimulated is shown in red; sessions in V4 was stimulated is shown in green. Right: TOJ error rates collapsed across sites and pre- and post- post tests demonstrate the TOJ error rate in the stationary and moving conditions. The black bar represents error rats for the moving condition and the white bar represents error rate for the stationary condition. Error bars represent the standard error.

There was an interaction between stimulation site and time ($F[2,18] = 3.587, p=0.049$, partial $\eta^2 = 0.285$), such that error rate increased after the dPMC and PPC were stimulated (dPMC: 27.00% to 32.75%; PPC:16.00 to 22.75, respectively), but decreased slightly at the control site (V4), (21.250% to 18.50%), which may reflect an overall small learning effect from pre-to post- conditions (see Figure 3.4).

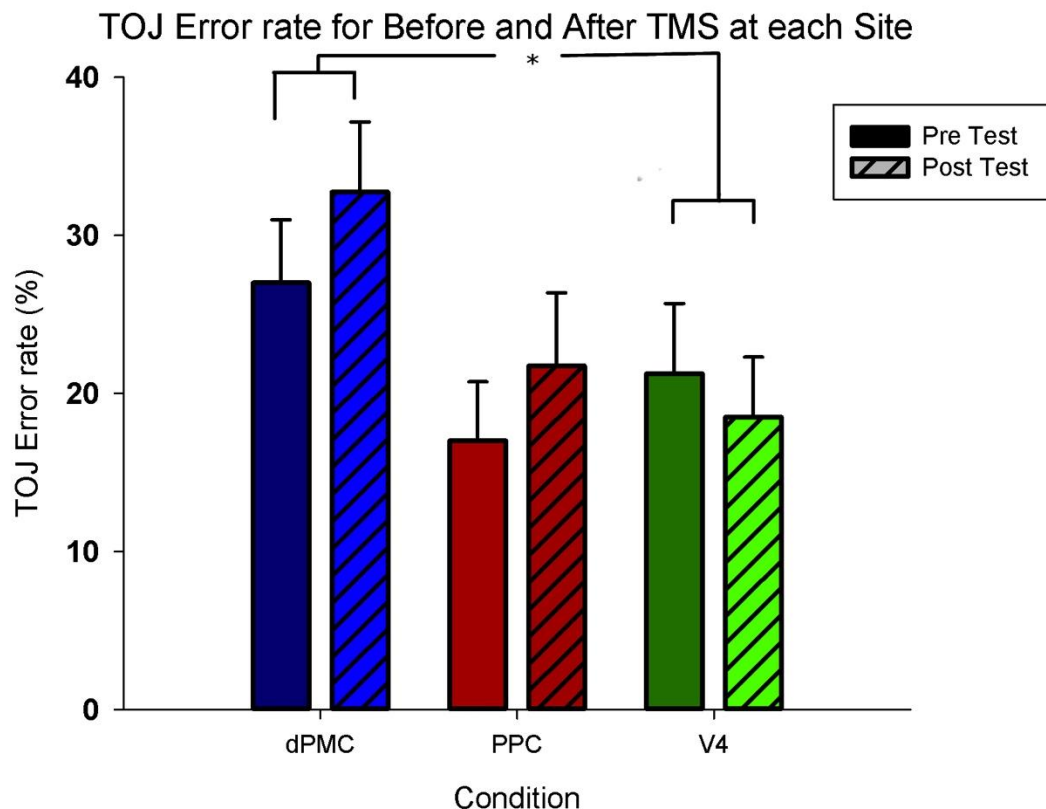


Figure 3.4: Changes in TOJ error rate from pre-test to post-test. Trials are collapsed across moving and stationary conditions as well as hand stimulated first. There was a significant interaction between the site

stimulated and whether the test was a pre-test or post-test. Solid bars indicate TOJ errors for the pre-test. Striped bars indicate post-test TOJ errors. Error bars: S.E.

We also observed a nearly significant 3-way interaction between the site, time, and hand, ($F[2,18] = 3.456$, $p=0.054$, partial $\eta^2 = 0.277$) such that error rates for the PMC increased for the right hand, but decreased for the left hand, compared to pretesting however, in the control site, we observed only a slight decrease following right hand stimulation and no change following left hand stimulation compared to pretesting (Figure 3.5). All other main effects and interactions were not significant.

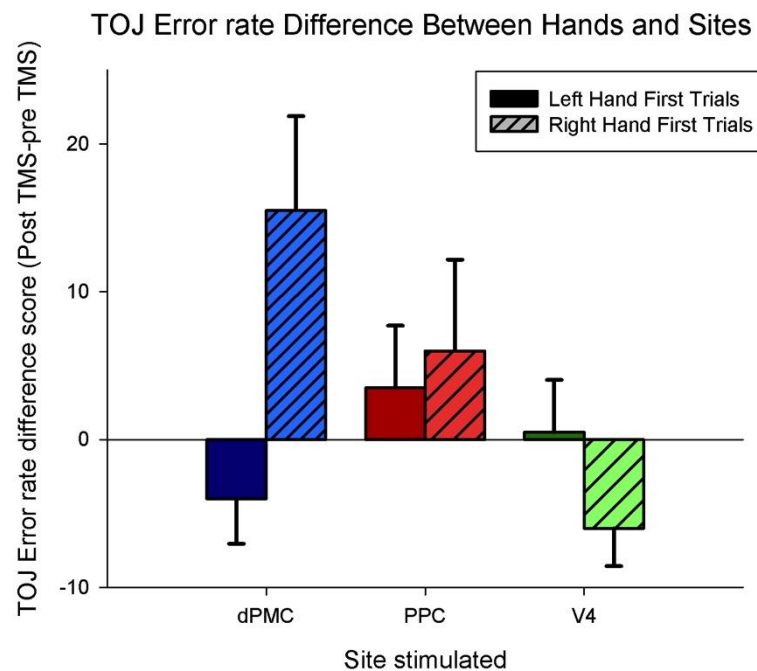


Figure 3.5: Change in TOJ Error rate from pre- to post-TMS across the 3 stimulation sites. Data from left (solid) and right (striped) hand stimulated first trials are shown separately. Error bars: S.E.

With this pattern of results we can now address specific hypotheses outlined in section 1.4.

Hypothesis 1a: When planning to cross the arms, error rates in the TOJ task following rTMS of the PMC will be decreased.

We were able to demonstrate that this hypothesis was supported - our findings indicated that rTMS over the dPMC significantly decreased the TOJ error rate when planning to cross the arms.

Hypothesis 1b: When planning to cross the arms, error rates in the TOJ task following rTMS of the PPC will be decreased.

We were able to demonstrate that this hypothesis was rejected - rTMS over the PPC induced an overall increase in overall TOJ errors, which suggests it is the PPC that is active in performing a spatially-defined TOJ task under either stationary or moving conditions.

Hypothesis 1c: When planning to cross the arms, error rates in the TOJ task following rTMS of the V4 will be unaffected.

This hypothesis was supported. TOJ errors were not statistically different after rTMS was applied to area V4, under moving conditions.

Hypothesis 2a: When not planning to cross the arms, error rates in the TOJ task following rTMS of the PMC will be unaffected.

This hypothesis was rejected. TOJ errors increased significantly after rTMS ipsilateral to the side where TMS was applied when PMC was targeted. This suggests that regions of PMC may encode ipsilateral spatiotopic coordinates.

Hypothesis 2b: When not planning to cross the arms, error rates in the TOJ task following rTMS of the PPC will be increased.

This hypothesis was supported. TOJ errors were statistically increased after rTMS was applied to PPC, when both stationary and moving conditions were considered. This suggests that

Hypothesis 2c: When not planning to cross the arms, error rates in the TOJ task following rTMS of the V4 will be unaffected.

This hypothesis was supported. TOJ errors were not statistically different after rTMS was applied to area V4, under stationary conditions. See section 4.1 for further interpretation of results.

3.2 Kinematic Analysis

We observed a significant increase in movement time in the left (contralateral) hand after the right dPMC was stimulated ($t(19) = -3.20$, $p < 0.01$). Additionally, there was a significant decrease in peak acceleration for the right (ipsilateral) hand. ($t(19) = 2.569$, $p < 0.01$). After the PPC was stimulated, there was a decrease in peak acceleration for both hands (right hand: $t(19) = 3.66$, $p < 0.05$; left hand: $t(19) = 2.23$, $p < 0.05$) and an increase in reaction time for both hands (right hand: $t(19) = -3.00$, $p < 0.01$; left hand: $t(19) = -3.41$, $p < 0.01$). Movement time of the left hand, but not the right, was also decreased after TMS over PPC ($t(19) = -2.62$, $p < 0.05$). After area V4 was stimulated, there was a small increase in the time to peak acceleration for the left hand ($t(19) = 2.20$, $p < 0.05$) as well as a small decrease in end point accuracy ($t(19) = -2.30$, $p < 0.05$) (see Table 3.3).

Table 3.3: Kinematics measured for arm crossing movements. Statistical comparisons were made using paired-samples t-tests, using a within-participant design. For a full breakdown of statistical comparisons, see Appendix B.

<i>Kinematic Variable</i>		<i>dPMC</i>			<i>PPC</i>			<i>V4</i>		
	Moving Hand	Pre	Post	Sig	Pre	Post	Sig	Pre	Post	Sig
Reaction time (ms)	Left	348.29	359.97	0.19	347.77	385.24	0.00*	346.38	348.83	0.84
	Right	337.10	351.03	0.17	345.60	380.00	0.01*	336.48	344.03	0.52
Movement time (ms)	Left	730.46	785.54	0.00*	676.21	743.98	0.02*	703.47	698.58	0.73
	Right	708.47	733.71	0.18	657.41	702.45	0.14	697.48	672.42	0.12
Peak Acceleration (mm/s ²)	Left	10221.20	9442.49	0.08	10949.33	10008.61	0.01*	10558.19	9879.90	0.10
	Right	9212.23	8295.86	0.02*	10142.17	9079.02	0.00*	10255.57	9659.56	0.07
Time to peak acceleration (ms)	Left	103.05	105.77	0.57	103.02	100.73	0.60	101.21	110.08	0.04*
	Right	113.20	105.17	0.20	105.74	105.46	0.95	104.18	105.10	0.80
Peak Velocity (mm/s)	Left	291.10	291.01	0.84	286.46	285.14	0.10	290.64	290.55	0.92
	Right	34.16	34.25	0.91	31.92	31.86	0.93	32.24	32.47	0.39
Time to peak velocity (ms)	Left	457.45	451.75	0.08	446.52	444.70	0.36	447.80	444.25	0.16
	Right	279.03	277.31	0.37	270.55	276.52	0.23	285.34	282.54	0.21
Peak deceleration (mm/s ²)	Left	42.60	50.09	0.24	39.16	38.34	0.69	35.70	37.01	0.46
	Right	144.93	148.34	0.19	149.65	145.36	0.12	144.56	143.44	0.44
Time to peak deceleration (ms)	Left	260.96	259.41	0.37	254.07	256.61	0.41	265.95	262.46	0.06
	Right	39.28	40.14	0.41	43.21	37.16	0.13	36.72	38.32	0.11
End pt. error (mm)	Left	32.09	34.07	0.39	45.80	39.42	0.19	27.91	33.18	0.03*
	Right	40.60	37.85	0.27	47.04	42.11	0.16	35.086	37.69	0.12

In addition to measuring accuracy, an end-point R^2 analysis (Heath et. al 2004) allowed us to evaluate the average explained variance of movement trajectory, within a particular trial condition. This form of analysis allows us to probe online control to determine during which

portion of the movement, corrections start to occur and whether movements are made in a ballistic or controlled manner. Time points with a very high proportion of explained variance reliably predict endpoint position, whereas those with lower explained variance do not predict end point position well and therefore are considered to be influenced more by online control. Figure 3.6 shows the proportion of explained variance quantified for each hand for pre and post conditions. R^2 values were subjected to a 3 (sites: dPMC vs. PPC vs. V4) by 2 (time: pre-test vs. post-test) by 2(hand: right vs. left) by 10 (each decile) 4-way RM ANOVA. We observed a significant effect of decile ($F[9,81] = 594.72$, $p < 0.001$, partial $\eta^2 = 0.985$). No other main effects were significant. We also observed a significant interaction between time and hand ($F[1,9] = 5.711$, $p = 0.041$, partial $\eta^2 = 0.388$), such that the explained variance for the right hand was significantly reduced after rTMS compared to the left hand. We observed a nearly significant 3-way interaction between site, time, and hand ($F[2,18] = 3.233$, $p = 0.063$, partial $\eta^2 = 0.264$). Additionally, there was a significant 3-way interaction between time, hand and decile $F[18,162] = 2.637$, $p = 0.001$, partial $\eta^2 = 0.227$. Post-hoc tests revealed that the proportion of explained variance was significantly reduced following PPC stimulation for deciles 5-10, however, this was not significant after a Bonferroni correction for multiple comparisons.

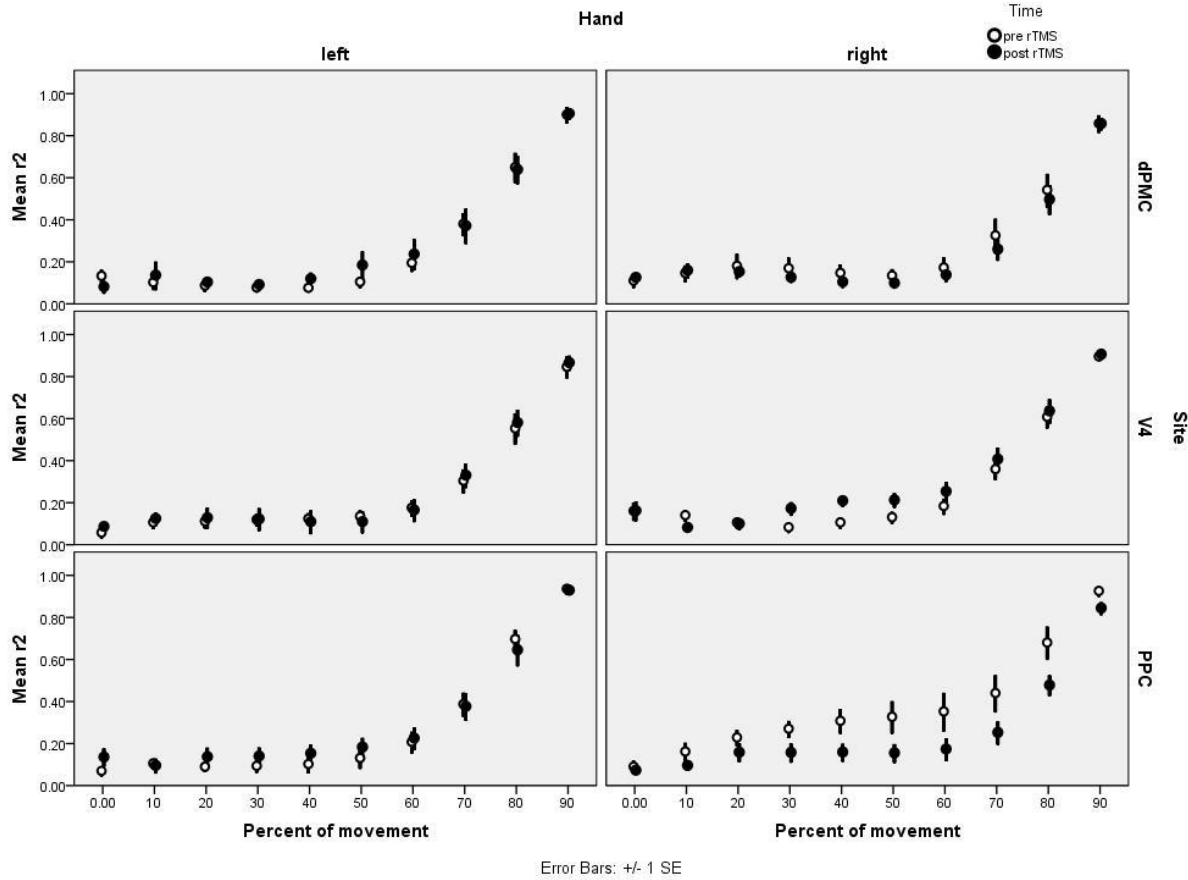


Figure 3.6: Explained variance of movement: R^2 analysis for movement trajectories. The proportion of explained variance at each decile of each movement. Decile were averaged based on trial type, then by participant. Open circles represent explained variance for pre-test conditions. Closed circles indicate explained variance for the post-test conditions. Error bars: S.E.

3.2 Sex Differences in TOJ performance

Previous experimental evidence has demonstrated that performance on TOJ tasks is worse among females compared to males when the arms are physically crossed compared to when the arms are physically uncrossed (Cadieux et. al 2010). We then examined the TOJ error rates using a 5-way mixed model repeated measures analysis of variance (RM-ANOVA) (2 [conditions: stationary vs. moving] x 2 [hand stimulated first: right vs. left] x 3 [stimulation site: PPC vs. PMC vs. V4] x 2 [time: pre-test vs. post-test] x 2 [sex: male vs. female]), with condition,

stimulation site, hand stimulated first, and time as within-participant factors, and sex as a between-participant factors. Statistical significance threshold was set at 0.05. We found no main effect of sex on overall TOJ error rates (females: 25.521 ± 11.356 vs. males: 21.389 ± 9.272 , $F[1,8] = 0.422$, $p=0.534$, partial $\eta^2 = 0.050$). We also observed a 3-way interaction between site, condition and sex ($F[2,16] = 7.214$, $p = 0.006$, partial $\eta^2 = 0.474$, such that during PPC stimulation session, females and males had a similar error rate under stationary conditions (females: 11.250 ± 11.701 vs. males: 7.083 ± 9.554), but females had a much higher error rate during moving conditions (females: 41.667 ± 11.05 vs. males: 19.583 ± 10.577). This finding may conflict with previous findings that demonstrate overall sex differences when the arms are crossed, however in our experiment, tactile stimuli were applied while the arms were still in the uncrossed posture. These seemingly disparate pieces of evidence could be reconciled if one were able to demonstrate differences in the way males and females prepare upcoming movements.

Chapter 4 - Discussion

4.1 General discussion of results

The present experiment was performed as a means of investigating cortical contributions to forward modeling by comparing performance on a TOJ task during the planning stages of movement before and after rTMS. The reduction of TOJ error rates contralateral to the site of stimulation when planning to move, suggests the PMC contributes to the prediction of the sensory consequences of movement. Normally, planning to cross the arms would cause an increase in errors in the TOJ task, but disruption of the PMC with rTMS muted the effects of the predictive process on the TOJ decision, causing a relative reduction in TOJ errors (see Figure 2.2) for moving trials. This was apparent via a comparison of the error rate change before and after rTMS is applied.

An overall increase in TOJ error rates was observed in both the stationary and moving conditions when the PPC was targeted with rTMS. There are multiple possible explanations for this result: it could be that the right PPC is necessary for resolving timing in general, or that the spatial limb localization necessary to perform both tasks is disrupted under both conditions. Although the PPC is also involved with predicting the sensory consequences of movement, because of its dense interconnectivity with primary sensory cortices, it is thought to retain a variety of somatosensory-based reference frames. If the PPC receives efference copy signals from the PMC to compare against existing spatial representations, error rates should increase following rTMS in both the moving and stationary conditions compared to pre testing. If under stationary conditions premotor activity is minimal, relatively little change in error rate from pre TMS to post TMS was expected. Because planning to move increases error rates for this task (Hermosillo et al. 2011), we predicted an increase under all moving conditions (i.e. regardless of

which brain region is targeted). With the disruption of efference copy signals, PMC TMS should induce an improvement in performance (i.e. TOJ error rates should decrease post- rTMS).

During PPC stimulation, we expected the error rates to increase relative to baseline if the PPC contributes to the spatial representation. With PMC TMS, we may again observe an improvement in performance, corresponding with the disruption of the forward model. In contrast to the PMC and PPC, because V4 is not directly involved in motor planning, we would expect similar error rate in both the pre and post test periods for both the stationary and moving conditions (Figure 2.2).

It is worth noting that we targeted the right PMC and PPC in our experiment because we have demonstrated previously that TMS over the right PPC induced a larger increase in error rates when the arms were stationary and crossed than TMS to the left PPC (Rosenbaum et al. 2014). By contrast, a study by Soto-Faraco and Azañón (2013) showed a strongly left-lateralized difference in EEG waveforms between crossed and uncrossed postures when tactile stimulation was applied. This difference was present soon after stimuli were presented (70-90ms) then briefly disappeared, and returned strongly 200 ms later, encompassing more parietal and frontal electrodes. Surprisingly, the left lateralized pattern was independent of the side of first stimulation. Furthermore, participants that demonstrated a larger conflict between reference frames showed a larger N80 negative shift in the left temporal and posterior electrode sites, suggesting that the regions of the left temporal lobe may be responsible for converting spatial reference frames. However, in the experiment outlined by Soto-Faraco and Azañón (2013), participants were performing a simple detection task with interleaved TOJs, which may have altered the pattern of fronto-parietal activation.

Even though the primary objective was to disrupt regions specifically associated with the prediction of the sensory consequences of movement, these regions are heavily connected with areas associated with producing motor output. Therefore, in addition to an alteration in TOJ errors during the planning phase of movement, we also observed differences in a number of kinematic markers. We know that TOJ error rates are modulated by reaction time (Hermosillo et al. 2011), and that reaction time is increased after TMS over the PPC (see Table 3.3). While this would explain the increase in error rate under moving conditions, an increase in TOJ error rate under stationary conditions was observed as well, suggesting that increased reaction time is not solely responsible for the increase in TOJ errors. Additionally, it is important to note that the vibrotactile stimuli were applied prior to movement, and that participants' error rates nevertheless increased.

End point correlation analysis revealed an increase in explained variance during the early phase of movement for the right hand after the PPC was stimulated. While this is ipsilateral to the side that is stimulated, there are two possible explanations for this: i) the right PPC subserves spatial processing for both limbs or ii) because the task involves bimanual movements, an efference copy is generated for each limb, and we may only be disrupting one.

Internal models are a widely theorized mechanism by which the CNS generates motor commands and/or makes predictions about future sensory and motor states. One such thoroughly ingrained construct is forward modeling. Forward modeling allows one to use motor plans to make predictions about upcoming sensory states. This has been investigated primarily in the field of eye movement research, but emerging evidence has also investigated how predictive signals are used from moving limbs. This experiment provides evidence of the existence of

forward models in healthy humans and demonstrates how and where they could be generated, and finally provides new constraints in our current understanding of predictive control.

The concept of motor prediction is sometimes interpreted differently among academics of different disciplines, and for this reason, Miall and Wolpert (1996) outlined specific types of forward models: a *forward dynamic model*, which estimates future system states after motor commands are executed, a *forward sensory model*, which predicts sensory signals from the current state, and finally, a *forward model of the environment*, which anticipates behavior in the external world. The *forward model of the environment* is established through a learned knowledge of world observation (e.g. the ability to predict where a ball will land after being thrown). In contrast, the forward dynamic model is established through a lifetime of world interaction, and is an unconscious process by which the body has learned to optimize. Here, a distinction in terminology is needed. We assume that the *forward dynamic model* is driven by the *effference copy*, and that this is used to inform the *forward sensory model*. In the context of this thesis, the term *corollary discharge* is used to describe predicted sensory signals. Lastly, the term *feed-forward* is sometimes used to describe general motor prediction in the brain, however, it is also used to describe many other homeostatic processes in the body, and is therefore considered too general for the purposes of this thesis and is avoided.

Previous adaptation studies have focused on how motor plans are altered over the course of a number of movements. Indeed, internal monitoring of movements is essential to learning any motor skill properly, and this typically is achieved through multiple attempts. This experiment attempted to reconcile the theoretical framework of forward models previously in the context of a particular movement, by attempting to establish how motor planning in the future

can influence current decision making. Previous work has examined how predictive motor planning is achieved in an intended movement (Hermosillo et al, 2011).

A distinction should be noted between generating an efference copy of intended movement and the volition to initiate a movement. Information can be used to inform predicted limb movements, but does not necessarily retain information related to computing desired kinematics. Once the intention to reach is generated, the inverse model transforms the kinematics of a desired limb movement into the kinetic signals required to achieve the desired muscle activation patterns (Shibuya et al. 2007; Wolpert and Ghahramani 2000). However, this simple plan-then-action mechanism is too incomplete to account for observed behavior. Humans move in a way that is far too coordinated to be expressed as a series of ballistic muscle contractions and too quick to be consciously adjusted for each movement. Anticipatory mechanisms recognized in humans for eye and hand movements, locomotion, and object manipulation have even inspired robotic researchers to employ these models to further accommodate the mechanical constraints of robotics (Barrera 2010). Emulating the movements of humans, especially the dynamic balance of bipedalism, has proven to be an enormous challenge for the field of robotics. It has only been within the last 2 decades that researchers have begun to incorporate internal models into movement plans to assist in generating smooth movements. This suggests that continuous updating based on minimum movement costs, and predictions are necessary computations present in both controlled movements of humans and robots. As a result, robots can produce anticipatory adjustments, based on executed movements.

The compensation between the expected sensory state that results from the motor command and the current sensory state is achieved through the creation of a simultaneous duplicate motor command, termed the efference copy, devoted to the prediction of the future

state of the limb (Wolpert et al. 2001; Wolpert and Ghahramani 2000). Originally investigated in the context of eye movements, the efference copy has proved to be a mysterious point of dispute. Translation of an efference copy through the forward model results in a signal that predicts the sensory consequences of the movement kinematics associated with the command that was sent to the muscles. This “expected kinematics” signal is compared to the actual sensory signals associated with the movement. By this means, the forward model overcomes the time delays associated with pure feedback control (Mulliken et. al 2008, Shadmehr and Krakauer 2008).

The idea that self-induced cutaneous sensation arising from movement, termed reafference, could be canceled using a subtractive comparison between efference copy and sensory signals was first proposed by von Holst and Mittelstaedt (1950). At the same time, Sperry (1950) was the first to use the term corollary discharge (CD) to describe a similar process. Both theories implied that the brain uses a copy of motor commands to predict the sensory consequences of movement. More recent research has provided evidence that the oculomotor system could make use of the expected sensory consequences of movement rather than the raw, unmodified efference copy (Haarmeier et al. 2001). The dynamics of the arm and sensory systems both contribute to the perceived sensory state of the limb, however, the state may not be actually known, only estimated, so there must be a functional distinction between state variables and sensed variables (see Figure 1.1). This is evidenced by the fact that changes in predicted limb configuration alter behavioral TOJs, but did not affect online correction movements (Figure 3.6).

Humans typically estimate the effector state via integration of multiple sources of information such as vision and proprioception, with the CNS ultimately using “higher” processed sensory signals rather than the direct information, garnishing the pertinent or situationally-

relevant information in an effort to minimize errors in the estimate. In Figure 1.1, we can see that the comparison of sensory signals and feedback delay (lower red summed junctions) produce a complete assessment of the motor system that can be used to make further adjustments, unanticipated by the forward model. Although forward models are justified from a theoretical point of view, and short-term adaptation studies (Shadmehr 2008) provide experimental evidence for their existence, the time course over which forward models have their influence during individual limb movements is less well understood. Behavioral evidence shows that even when participants reach while an external force is applied to their limb, if the force is abruptly introduced, large errors result, however when the perturbation is gradually introduced, performance errors are small, suggesting that the forward model for reaching includes an internal model of the arm as well as an internal model of the manipulandum used for adaptation (Kluzik et al., 2008).

The present study is novel to the extent that few studies have attempted to assign processes of forward modeling to anatomical structures in humans (Miall et al., 2007). Evidence for the existence of these mechanisms is more substantial from research in other animal species. One of the more interesting examples of corollary discharge comes from the mormyrid electric fish. The fish uses a specialized receptor for electric signals called the knollenorgan to detect its own electric organ discharges when communicating with other fish (Bell 1989). The fish uses the organ to modulate sensory reafference, preventing confusion between self-generated electrical signals and external sensory signals (Bell 1989) Emerging behavioural evidence suggests that humans are also capable to sensory gating to avoid the introduction of sensory noise during movement (Buckingham et al. 2010) .

A similar process has been observed in the human visual system. Evidence suggests that the brain uses oculomotor plans to remap retinal space in anticipation of movement for the purposes of stabilizing the visual world even under the context of constantly moving eyes. One such way to investigate such remapping is by using a double-step saccade task. In a double step-paradigm, participants are presented with two targets in quick succession and asked to generate a saccade to each target in the proper order. Because the targets are illuminated and extinguished prior to the first saccade, the participant must make both saccades in complete darkness. Importantly, whereas the first saccade can be generated based on retinal signals, the second saccade must use both retinal signals as well as a signal corresponding to the characteristics of the first saccade. The fact that participants can normally generate accurate saccades to the locations of both previously presented targets (Becker and Jürgens 1979) is consistent with the fact that the visual receptive fields generated by the retinal signals are remapped in anticipation of movement (Duhamel et al. 1992). Single-unit recordings in the medial dorsal nucleus of the thalamus in monkeys confirm that a copy of motor commands is sent from the superior colliculus to remap receptive fields within the frontal eye fields (Sommer and Wurtz 2002; Sommer and Wurtz 2006). Furthermore, when these thalamic neurons are inactivated, the second saccade in the double saccade sequence is deviated in a manner consistent with a disruption to the internal monitoring of the first saccade. Therefore, good evidence for spatiotemporal coherence between neurons with shifting receptive fields and corollary discharge exists at least for the visual system. By extension, this points out the clear need for internal monitoring of moveable sensory organs within the somatic system. Indeed, the results from the TOJ arm crossing task (Hermosillo et al., 2011) are consistent with the fact that the brain internally monitors planned limb movements and this can influence perceptual decisions regarding the timing of cutaneous stimulation at the

fingers. Moreover, the results from the current study demonstrate that these processes map onto specific regions of the brain.

4.2 The Role of the Posterior Parietal Cortex in Movement Planning

Most of what is known about the functions of the PPC arises from nonhuman primate studies, primarily the macaque, because even though diffusion weighted imaging can be used in humans to follow bundles of cortico-cortical axonal tracts, single axonal tracings cannot be easily obtained from living humans. However, structural MRI has shown that these cortical structures are only roughly similar across species (Zilles et al. 2003). Recurrent fronto-parietal connections have been observed, many of which eventually synapse on neurons forming the corticospinal tract, providing strong evidence for PPC involvement with the sensory-motor transformations requisite for motor planning. These reciprocal connections consequently provide some room for debate as to the exact role of the PPC in planning and execution versus only providing a mechanism from which plans can be made (Anderson 1997). Generally the anterior portion of the parietal lobe is thought to retain primarily functions pertaining to somatosensory perception, whereas the PPC is a multimodal integration center associated with using this information along with visual and other relevant sensory signals during motor control. Thus, the PPC is an ideal candidate site where spatial and temporal processing becomes of vital importance, especially as they relate to movement planning. Mulliken and colleagues (2008) showed, using multiple single unit recordings in a monkey, that the PPC contains a forward estimate of the movement state. Neurons in this area encode both static target direction and dynamic movement angle of the limb. Characterizing the encoding properties of the neurons, they were able to construct a space-time tuning function (STTF). The function can be applied to neurons in PPC to characterize what movement state is represented (past, present, or future) through analysis of

mutual information of the target angle and movement angle. The temporal encoding properties of movement-angle neurons strongly suggest that the PPC helps to compute a future state estimate, which is related to the current findings suggesting that the PPC is essential for current state estimation. Because these neurons encode the movement angle of the effector, it is reasonable to assume that this information could be used to construct a state estimate for a single effector (e.g. an intrinsic hand representation). If this representation is determined by the efference copy, then one could theoretically also use it for stabilization of the external world, much in the same way the visual stabilization across eye movements is contingent on corollary discharge. While Mulliken and colleagues (2008) used single-unit recordings in monkey PPC, the current experiment demonstrates that this same process occurs in humans in the same region, and can be disrupted non-invasively.

Movements can be made with respect to the whole body, individual body segments, eye position, the environment, and up-coming movements, and accordingly, neurons in various brain regions process each, or combinations of these reference frames. However, the current results suggest that at least the PPC, encodes hand and spatial reference frames, which is consistent with previous literature (Lloyd et al. 2003). Indeed, the presence of multiple reference frames and the necessity of each one contextually may help account for the differences observed between planning arm crossing compared to uncrossing (Hermosillo et al. 2011). To investigate if the planning of movements would influence the perception of incoming cutaneous stimuli, participants performed judgments about the temporal order of successive cutaneous stimuli applied to each index finger. Yamamoto and Kitazawa (2001) and Shore colleagues (2002) showed that the ability to localize stimuli was impaired during short intervals and, as a result, participants often reported that the opposite hand was stimulated when the arms were crossed.

These findings also suggest that the brain may attempt to use a body representation of the uncrossed posture while simultaneously attempting to use a conflicting hand representation of the crossed posture (Figure 2.1 B). That is to say, the spatial representation based on upcoming movement plans conflicts with the actual spatial configuration of the arms. Amazingly, the change in error rates directly reflected the movement context. And furthermore, the weighting of the representations is dependent on the amount of time available to plan. In particular, the further into the planning process participants were, the more their TOJ error rates resembled that of their final posture (Hermosillo et al. 2011).

4.3 Cerebellar contributions to modeling

Our results suggest that the PPC is involved with processing of an efference copy signal possibly arising from the premotor cortex or cerebellum, both of which have substantial reciprocal anatomical connections with the PPC. This processing contributes to the mitigation of an otherwise incomplete motor model due to the large feedback delays associated with afferent feedback. These delays can be overcome by use of internal predictive representations of the motor effector. Miall and Wolpert (1995) have suggested that the cerebellum is a likely site for comparison of expected and actual sensory feedback. They suggest that the cerebellum acts as a “Smith Predictor”, which contains two neural models—one a representation of the motor apparatus, which can be theoretically used to predict the sensory consequences of the movement; and a second which accounts for the time delays associated with sensory feedback. The Smith Predictor reconciles these two, in an attempt to give an error signal to ensure that any unexpected sensory information is recognized. Comparison allows for discrimination between external and internally-induced sensory changes. The latter model may be supplied to the cerebellum for comparison after lower-level sensory stimuli are compiled in the PPC. In this way, the expected

kinematics can be compared against actual kinematics (Figure 1.1). The present experiment investigated the construction of an internal representation of the effectors required to form a state estimate. The change in increase in error rate in Figure 3.1 after rTMS over the PPC suggests, but further research is required to demonstrate conclusively, that the PPC contributes to the forward model by providing a sensory estimate of the motor system while moving, theoretically formed from the efference copy. The cerebellum however is often implicated as the comparator for error correction in the brain, especially considering the sequelae (mild ataxia and intention tremor) observed in patients with cerebellar damage. The cerebellum does seem to be crucial to motor learning, on-line adjustments, and state estimation (Miall 2007). If we examine Figure 1.1, we can observe that the forward and inverse models can exist independently. In Figure 1.1, cerebellar processes are hypothesized to perform the error detection (junction summations in red “X”s) due to cytoarchitecture and established cortical connections. Given the cytoarchitectonic structure of the cerebellum, we expect that after the expected sensory consequences of movement are computed in the PPC, (including its latency delay) and the neural signals travel through the pons to the cerebellum, the signal is nearly identical to actual sensory feedback, at which point error correction can be determined to update the current state estimate in the parietal cortex via the thalamus. Because of the complex orchestration of this process to compensate for changes in sensory and motor feedback, and constant sensory-motor adaptation a working mechanism that showed direct electrophysiological linkages between these cortices would prove indispensable in unraveling this complex, multifaceted process. Other studies have also shown PPC contains temporal and spatial information relating to the forward estimation of movement state (Mulliken et al. 2008). Typically, efference copy is thought of as a necessary computation in order to allow for rapid online correction of motor outputs. This copy of the motor plan can be used to predict

the upcoming movement and the resultant sensations. The corollary discharge produced by the efference copy could also be used to cancel out the signals received by sensory neurons in the periphery.

The efference copy could, theoretically, be used to inform other psychological processes such as agency. Agency, the idea that we can distinguish self from other, can also be defined in terms of physiological feedback, such as ensuring that humans can distinguish active movements from passive movements, from an arm moving across a table versus feeling a table moving under a stationary arm. Sommer and Wurtz (2008) propose that one of the most subtle, yet highly necessary roles of corollary discharge is the stabilization of the visual array in organisms that have movable organs through which one observes the world.

4.4 The role of the premotor cortex in movement planning and prediction

Neurons in the premotor cortex have been shown previously to become active prior to movement onset. Exactly what premotor neurons are encoding in preparation for movement is still unclear, but evidence suggests these neurons code for eye, hand, and goal reference frames (Peseran et al. 2006), and that the neural activity during the period prior to reaching even predicts reaction time (Churchland et al. 2006). While there exists plenty of evidence that neurons in premotor cortex are responsible for movement planning and preparation, there is little evidence that they generate an efference copy signal, other than anatomical evidence that shows strong connections with parietal reach regions (Tanne-Gariepy et al. 2002). One major piece of evidence comes from electrical stimulation of patients undergoing brain surgery (Desmurget et al. 2009). In this experiment, patients were stimulated in the premotor cortex, which elicited mouth and contralateral limb movements which the patients firmly denied occurring. There are a number of possible explanations for this: one of which is that when a reach plan is not generated,

stimuli related to self movement are not recognized, another is that even though a muscle command can be sent to the limbs through exogenous stimulation, that doesn't necessarily mean that an efference copy is generated. The present results suggest that the premotor cortex is capable of parallel processing by motor commands sent to the muscle for movement, as evidence by the fact that participants are still able to initiate movement (Figure 3.6), but still improve in TOJ performance after rTMS (Figure 3.5 – dark blue bar).

One pathway that has been investigated, at least in monkeys, has been corollary discharge in saccadic eye system. Researchers inactivated the pathway leading to a frontal region (frontal eye field, or FEF) associated with generating saccades in the superior colliculus (Sommer and Wurtz 2002). Monkeys performed a double-step saccade task as described previously (see section 4.1 – General discussion of results). Before inactivation, monkeys made accurate saccade sequences, however after inactivation of the efference copy pathway, saccades to the second target were much less accurate, suggesting that monkeys had difficulty using the output associated with the 1st saccade to plan and execute the 2nd saccade. However, the parallels of the saccadic eye system with the limb system should be viewed cautiously, because even though the FEF seems to serve an analogous role for the oculomotor system as the premotor cortex does for the limb system, there are many differences between how these neurons encode information and relay information to their respective target executor regions.

4.5 Posterior parietal contribution to temporal perception

As a location to process reafference, it logically makes sense that coincidence detectors should be used within the computational motor planning model to compensate for a time delay, and that this detection mechanism can be referred to for information about successive events. However, one theory presented by Walsh (2003) suggests that portions of the parietal lobe,

particularly the inferior parietal lobule code information with respect to space, time, and quantity to provide answers to questions related to desired kinematics such as, “How far...?”, “How big...?”, and “How fast...?”. Sigiru and colleagues (2004) have shown that patients who have damage to the parietal lobe display an altered awareness of voluntary action, such that maintaining or creating these internal models used to inform movement are compromised and the latencies associated with state estimation are removed.

How do we know that the PPC lies at the interface between visuospatial processing and action? Patients with unilateral spatial neglect (also called hemi-inattention or simply left/or right neglect), suffer from disrupted spatial attention for stimuli presented typically to the left side of space. In patients with spatial neglect, attention, but not spatial perception is shifted to the right (Posner 1984). Interestingly, patients with spatial neglect show that only certain portions of space are lost without affecting the ability to identify objects as a whole. Kinsborne (1977) suggests a vector model of spatial attention contingent on a balance of cortical activation and inhibition between parietal lobes, such that a unilateral lesion would shift attention to the side opposite to the site of damage. To those with typical visual perception, this idea that certain sections of space cannot be perceived is unsettling, because of the automated nature of integration of the visual array and awareness of the objects within it. Given the nature of their deficits and the contribution of the PPC to sensorimotor transformations, it is apparent that spatial neglect patients would have difficulty constructing reference frames. Therefore, it appears that a crucial component of temporal-spatial perception coexists in the attentional network. One potential interpretation of the rTMS applied in the current study is that it induced transient virtual spatial neglect-like performance in participants, whereby they were unable to attend to that particular region of space.

The right hemisphere seems to be particularly important for spatial processing and attention associated with movement. Vesia and colleagues (2008) have shown that TMS over the dorsal-lateral PPC systematically disrupts memory-guided reaching indicating that this area is essential for computing a reach vector or the internal representation of the hand position required to calculate such a vector. They also showed that this hand representation can be updated at any point in the movement. One interesting aspect of their study that is reinforced by others, is the subtle, yet observable interhemispheric differences between the right and left PPC functions (Oliveri et al. 1999, Vesia 2008, Woo 2009). In particular, TMS over the left PPC increased endpoint variability, whereas TMS over the right PPC appeared to impart a left-ward directional shift, suggesting each PPC contributes differently to reaching. The present experiment targeted the right PPC specifically, which has been shown contribute significantly to reconciling spatially-localized tactile stimuli (Ritterband-Rosenbaum et al. 2014).

Spatial reference frames are hypothesized to be based on a number of modalities, such as hand-centric, eye-centric, whole-body centric or even environmentally-based. Lloyd and colleagues (2003) have shown that reference frames can shift across space as needed. They showed that tactile stimulation of the right hand on the left hand side of space activates the right posterior parietal cortex when the eyes are closed and shifts to the left parietofrontal network when the eyes are open. Additionally, non-dominant (left) hand stimulation showed a more bilateral activation pattern when the eyes were open, whereas stimulation of the left hand across the midline with eyes closed biased activation toward the right premotor and parietal cortices compared to the eyes-open condition. These findings suggest that vision plays a central role in modulating perceived limb position, but also that tactile, proprioceptive reference frames activate different neural networks when vision is absent. This evidence is supported by Desmurget and

colleagues (2009) who demonstrated that electrically stimulating the parietal region in patients undergoing brain surgery resulted in the feeling that the contralateral arm had moved despite the lack of EMG activity, which may indicate that spatial reference frames for reaching are housed within the PPC, which is consistent with the increase in contralateral error rates after rTMS was applied to the PPC (Figure 3.5, central bars). This deep electrical stimulation may be mimicking the necessary efference copy signals to elicit a moving sensation.

4.6 Sensory attenuation and mislocalization

The current experiment also provides insight into another line of research which has shown that, while moving, sensory signals are attenuated possibly to dampen the effect of the large increase in afferent activity that occurs (Voss et al. 2008) or so that incoming sensory signals can be distinguished from expected sensory signals, thus, allowing differentiation between self-induced changes in sensory state from external sensory stimuli. This attenuation of sensory signaling appears to start about 50ms prior to movement, indicating that anticipated movements dampen sensory signals.

Dassonville (1995) examined the concept of haptic mislocalization of tactile stimuli during movement, suggesting that it might be due to an inaccurate representation of the hand movement, a lack of a mechanism to register the appropriate timing information, or both. This mislocalization tends to be in the direction of movement, which indicates that perception is influenced the unconscious planning in the motor control. Watanabe and colleagues (2009) have addressed the idea of systematic haptic mislocalization before, during, and after movements, questioning the failure of sensory-motor integration process. They found clear differences in haptic localization when participants were given stimuli that were on then turned off, or off and then turned on. When participants reported the vibration onset, mislocalization was in the

direction of movement, however, when participants responded to the vibration *offset*, localization shifted away from the direction of movement. They suspect that the temporal information about contact plays a vital role in spatio-temporal coherence. This suggestion allows one to explain mislocalization in terms of forward modeling, but also may suggest that events that happen in the past might also be inferred improperly, given a set of motor commands.

4.7 TMS Electrophysiology

While many studies have used TMS as an investigative tool there have been relatively few studies that have attempted to determine the behavior of neurons subjected to an electromagnetic field. It has been established that the electromagnetic field causes an alteration in neuron firing, however, how an individual neuron re-establishes resting membrane potential (RMP) in response to the field is unclear. A few studies have attempted to determine how an individual neuron “recovers” from TMS or even if the mechanisms that follow may induce depolarization are indeed different from intrinsic firing. Only now have a few modeling studies attempted to address the conduction properties of various magnetic fields on conductive tissue, and even these simply assume uniform conductive properties of the entire head (essentially a water-balloon). Even when the aforementioned assumptions are true, many studies examine the electrophysiology of neurons using M1. Many studies, including this one, assume that the magnetic field strength necessary to alter neural behavior in M1 is sufficient to alter neural behavior in other cortical regions. However, until a readily-observable physiological litmus test of neural stimulation is discovered instead of a muscle twitch, TMS studies are resigned to scale cortical stimulation to M1 neural behaviour.

Consequently, we may not be able to say with any certainty that when a specific region of the motor area is coaxed into firing, that this replicates any natural bodily process. When

planning signals that correspond with motor output that are generated simultaneously are not produced as they would typically be produced, downstream areas that receive sensory information, may now be “surprised” by self-motion that isn’t internally generated. How these errors are encoded has not been investigated.

One question that logically follows from using TMS to disrupt a specific region of cortex is, “What happens to functionally connected tissue when TMS is applied?” Shitara and colleagues (2011) addressed this issue by performing TMS while simultaneously measuring brain activation using fMRI. Their experiment revealed that TMS generates the canonical hemodynamic response function observed in conventional fMRI experiments. When M1 was stimulated, they were able to demonstrate that TMS effects not only local cortical tissue, but remote motor areas, specifically those that are densely connected with M1, and furthermore that the induced motor output can cause regional BOLD (blood oxygen level dependent) signal in afferent regions resembling that occurring with median nerve stimulation. This experiment provides very clear evidence of the complexity of TMS and the potential dangers of assuming specific regional stimulation.

However, we must consider an additional assumption of the binary affects of TMS, which asks whether TMS excites or inhibits neurons. This is a complex question because numerous studies have demonstrated the inhibitory or “deleterious” effects on behavioural performance, however clearly application of TMS to the primary motor cortex produces an observable muscle twitch where there was none before. Theoretically, one way to explain these seemingly contradictory findings is that embedded in the motor cortex are populations of inhibitory neurons preventing the spontaneous generation of motor output and that these neurons are inhibited by TMS. If this was indeed the case we must either expect that they outnumber excitatory motor

neurons or exert a collective inhibition greater than the excitation generated by the local population. The factors affecting the spontaneous discharge rate of a population of neurons are numerous. Among these are RMT, previous firing, distribution of neuron types, and local network anatomy. But importantly, discharge rates are heavily influenced by network *behavior*. *In vivo* single unit recordings in cat V1, have demonstrated that after rTMS neurons displayed significant phase-decoupling within the region (Allen et al. 2007). This suggests that regional function can no longer produce the emergent behavior from local populations of neurons. Theoretically, this would explain why task performance declines on behavioral tasks, and fMRI activation within those regions can no longer be observed (Pascual-Leone et al. 2005). The present experiment assumes a similar disruption of coordinated network behavior necessary for meaningful emergent regional neural function. That is to say, neurons within the PPC might not necessarily be more or less excitable in way that describes motor neurons, but may still be recovering from the magnetic field. It is clear that the neural populations in these regions have altered their firing pattern as evidenced by the behavioural changes shown in Figure 3.2, but how they have changed is not readily apparent.

Chapter 5 - Conclusion

The results from the current study inform current theories of time and spatial perception in humans and its importance in motor planning. Components of this work are applicable in many settings, particularly in sensory deficit individuals, and in limb motor planning both in terms of the details of the predictive planning process and the nature by which this process is implemented in the brain. In particular it has been demonstrated that stimulation of the PPC induces a disruption in spatial processing necessary for motor control, and additionally, that efference copy signals that are used to make predictions regarding movement can be disrupted, without disrupting movement kinematics. Additionally, while behavioral evidence in humans and animals studies suggest forward modelling encoding by neurons, no studies have tested the physiological underpinnings of efference copy generation in healthy humans through TMS. Given that particular elements of information processing are used to guide the development of rehabilitative interventions for patients with sensori-motor deficits, the results from these experiments will increase the knowledge base from which those developing such interventions can draw, and ultimately make the interventions more successful in improving the daily lives of patients afflicted with brain injury. In this manner, rehabilitation for patients with dysmetria can target specific aspects of movements, for example, emphasizing proprioceptive estimation.

Forward models are developed through a lifetime of sensory prediction and error correction. This experiment provides evidence that the sensorimotor areas that are used for prediction are also use in the development of balance and loss of motor control with an emphasis on stroke and other motor diseases. While this experiment has provided clear evidence for spatial processing in the context of motor control, further research is needed to determine how unified space is constructed in the brain.

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APPENDIX A: FULL STATISTICAL ANALYSIS of KINEMATICS

Table A.1: Full statistical comparison of kinematics. Each measurement was treated an independent variable subjected to a 4-way RM ANOVA (See “Methods” section for details).

Kinematic Variable		dPMC			PPC			V4		
	Moving Hand	Pre	Post	Sig	Pre	Post	Sig	Pre	Post	Sig
Reaction time (ms)	Left	348.29	359.97	0.19	347.77	385.24	0.00	346.38	348.83	0.84
	Right	337.10	351.03	0.17	345.60	380.00	0.01	336.48	344.03	0.52
Movement time (ms)	Left	730.46	785.54	0.00	676.21	743.98	0.02	703.47	698.58	0.73
	Right	708.47	733.71	0.18	657.41	702.45	0.14	697.48	672.42	0.12
Peak Acceleration (mm/s^2)	Left	10221.20	9442.49	0.08	10949.33	10008.61	0.01	10558.19	9879.90	0.10
	Right	9212.23	8295.86	0.02	10142.17	9079.02	0.00	10255.57	9659.56	0.07
Time to peak acceleration (ms)	Left	103.05	105.77	0.57	103.02	100.73	0.60	101.21	110.08	0.04
	Right	113.20	105.17	0.20	105.74	105.46	0.95	104.18	105.10	0.80
Peak Velocity (mm/s)	Left	291.10	291.01	0.84	286.46	285.14	0.10	290.64	290.55	0.92
	Right	34.16	34.25	0.91	31.92	31.86	0.93	32.24	32.47	0.39
Time to peak velocity (ms)	Left	457.45	451.75	0.08	446.52	444.70	0.36	447.80	444.25	0.16
	Right	279.03	277.31	0.37	270.55	276.52	0.23	285.34	282.54	0.21
Peak deceleration (mm/s^2)	Left	42.60	50.09	0.24	39.16	38.34	0.69	35.70	37.01	0.46
	Right	144.93	148.34	0.19	149.65	145.36	0.12	144.56	143.44	0.44
Time to peak deceleration (ms)	Left	260.96	259.41	0.37	254.07	256.61	0.41	265.95	262.46	0.06
	Right	39.28	40.14	0.41	43.21	37.16	0.13	36.72	38.32	0.11
End pt. acc (mm)	Left	32.09	34.07	0.39	45.80	39.42	0.19	27.91	33.18	0.03
	Right	40.60	37.85	0.27	47.0421025	42.11400265	0.16	35.08598251	37.68781847	0.117226478

Kinematic Variable	ANOVA Variable	site	pre	post	hand first	site*pre	post	site*hand first	Pre	post*hand	site*pre	post*hand
	DOFs	F[2,18]	F[1,9]	F[1,9]	F[2,18]	F[2,18]	F[2,18]	F[1,9]	F[2,18]	F[2,18]	F[2,18]	F[2,18]
Reaction time (ms)	Left		0.393 (0.680)	2.753 (0.131)	2.503 (0.148)	2.846 (0.084)	3.191 (0.065)	1.875 (0.204)	0.278 (0.761)			
	Right		0.572 (0.575)	2.977 (0.119)	0.960 (0.353)	1.626 (0.224)	4.791 (0.021)	4.673 (0.059)	0.181 (0.836)			
Movement time (ms)	Left		2.994 (0.75)	5.461 (0.044)	0.203 (0.663)	2.087 (0.153)	0.875 (0.434)	0.250 (0.629)	0.387 (0.685)			
	Right		2.852 (0.084)	1.098 (0.322)	1.017 (0.340)	1.257 (0.308)	0.266 (0.769)	0.652 (0.440)	0.097 (0.908)			
Peak Acceleration (mm/s^2)	Left		0.725 (0.498)	10.529 (0.010)	0.003 (0.959)	0.067 (0.936)	0.3226 (0.063)	2.017 (0.0189)	0.434 (0.654)			
	Right		1.147 (0.340)	9.498 (0.013)	1.340 (0.277)	0.388 (0.684)	3.498 (0.052)	0.436 (0.526)	0.230 (0.797)			
Time to peak acceleration (ms)	Left		0.413 (0.668)	0.569 (0.470)	0.372 (0.557)	1.388 (0.275)	1.034 (0.376)	0.135 (0.721)	0.410 (0.670)			
	Right		0.415 (0.667)	0.924 (0.361)	4.631 (0.060)	0.522 (0.602)	0.161 (0.853)	0.214 (0.655)	0.475 (0.629)			
Peak Velocity (mm/s)	Left		0.570 (0.576)	14.399 (0.004)	0.529 (0.485)	1.086 (0.359)	3.520 (0.051)	1.264 (0.290)	1.139 (0.342)			
	Right		0.693 (0.513)	9.175 (0.14)	0.002 (9.69)	0.569 (0.576)	2.398 (0.119)	0.101 (0.758)	2.149 (0.146)			
Time to peak velocity (ms)	Left		1.419 (0.268)	1.701 (0.224)	4.819 (0.056)	0.050 (0.952)	0.915 (0.418)	0.277 (0.611)	0.685 (0.517)			
	Right		1.378 (0.277)	0.264 (0.620)	0.906 (0.366)	0.244 (0.786)	1.438 (0.264)	1.057 (0.331)	0.306 (0.740)			
Peak deceleration (mm/s^2)	Left		0.096 (0.909)	12.223 (0.007)	1.436 (0.261)	0.764 (0.480)	8.614 (0.002)	3.069 (0.114)	0.966 (0.399)			
	Right		0.772 (0.477)	5.436 (0.045)	2.728 (0.133)	2.642 (0.099)	1.167 (0.334)	0.836 (0.384)	0.926 (0.414)			
Time to peak deceleration (ms)	Left		0.513 (0.607)	2.747 (0.132)	0.210 (0.657)	0.598 (0.561)	0.149 (0.863)	1.1014 (0.340)	0.755 (0.484)			
	Right		1.152 (0.338)	4.694 (0.058)	1.328 (0.279)	0.647 (0.535)	0.749 (0.487)	1.915 (0.200)	0.497 (0.616)			
End pt. acc (mm)	Left		2.115 (0.150)	0.023 (0.883)	0.468 (0.511)	1.387 (0.275)	3.369 (0.057)	0.000 (0.990)	1.411 (0.270)			
	Right		1.179 (0.330)	0.706 (0.423)	0.893 (0.369)	1.377 (0.278)	1.206 (0.323)	1.108 (0.035)	0.769 (0.478)			